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Effects of THIP on Chronic Anxiety

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Abstract. The effects of THIP, a GABA agonist, were examined in patients with anxiety disorders. Eight patients were prescribed THIP (5–20 mg) to be taken three times a day for 2 weeks in a single-blind study, with placebo conditions preceding and following the active drug period. Anxiety ratings significantly decreased on several measures during active drug treatment and increased again with placebo administration. However, the anxiolytic effects of THIP appeared to be weak and occurred at, or close to dose levels which induced sedation and undesirable side effects. As with other GABA agonists and GABA-mimetic drugs, side effects included giddiness, depersonalization, poor concentration, and transitory delirious states, suggesting that excessive stimulation of the GABAergic system may disrupt normal brain functioning.

Key words: GABA – GABA agonists – THIP – Anxiolytics

Recent studies have suggested the involvement of the GABAergic system in the regulation of anxiety responses (Tallman et al. 1980; Hoehn-Saric 1982a). It has been assumed that the anxiolytic effects of benzodiazepines are mediated through a link between the benzodiazepine receptor and a GABA recognition site which forms the GABA-benzodiazepine-chloride ionophore complex (Paul et al. 1981). In this complex, benzodiazepines do not act as GABA agonists, but enhance the effects of GABA. Therefore, it appears reasonable to assume that an increase of GABAergic activity in the brain would have anxiolytic effects. However, animal studies have only partially supported this assumption. The increase of GABA levels in the rat forebrain through the administration of GABA-transaminase inhibitors (drugs that block the catabolic enzyme of GABA) failed to affect avoidance responses in conflict tests (Palfreyman et al. 1981) or to enhance novel food consumption in rats (Hodges and Green 1981). These compounds also failed to increase the anxiolytic effects of benzodiazepines, although they enhanced their sedative effects (Palfreyman et al. 1981). Cuomo et al. (1981) found the GABA agonist muscimol effective in conflict tests, but the action of muscimol was not identical to diazepam. Thiébot et al. (1980) reported that muscimol failed to reduce behavioral suppression and did not potentiate the 'disinhibitory' effects of diazepam. Thus, it is questionable that all effects of benzodiazepines are mediated through the GABAergic system. In humans, muscimol in low doses was found to sedate and calm some schizophrenic patients, but high doses increased psychotic manifestations (Tamminga et al. 1979).

THIP, a 4,5,6,7-tetrahydroisoxazolo (5,4-C) pyridin-3ol, is a muscimol analog which exhibits specific GABA-agonists properties without affecting enzymes involved in the synthesis or the catabolism of the neurotransmitter. It is 5–15-times weaker than muscimol and substantially less toxic. THIP penetrates the blood-brain barrier and has a half-life of 1.5–2 h (H Lundbeck and Company 1981). It differs from muscimol by not enhancing benzodiazepine binding at 0° C, but at temperatures of 30°–37° C (Supavilai and Karobath 1980). These differences are explained through the molecular structure of THIP, which is more rigid than the structure of muscimol. It appears that rigidity of molecular structure is inversely related to the compounds' ability to potentiate benzodiazepine binding (Krogsgaard-Larsen and Arnt 1980). Additionally, THIP may bind only to certain GABA recognition sites (Falch and Krogsgaard-Larsen 1982). In animals, THIP produces muscle relaxation and sedation, although to a lesser extent than diazepam. THIP has anticonvulsive properties in combination with substances that induce convulsions by limiting GABA synthesis or are specific GABA antagonists, such as bicuculline. In contrast to diazepam, THIP fails to inhibit convulsions induced by electrical current, noise, or photic stimulation (H Lundbeck and Company 1981). Furthermore, reports on THIP in animal conflict tests are contradictory. No effects (Rasmussen et al. 1981), nonspecific effects in dosages which create sedation (H Lundbeck and Company 1981), and positive effects (Cananzi et al. 1980) have been reported.

To date, GABA agonists have not been examined for their anxiolytic properties in humans. The purpose of this study was to investigate, in a single-blind design, the effects of the GABA-agonist THIP on patients with chronic anxiety disorders. THIP was selected because it is less toxic than muscimol and because it is a standard drug used in pharmacological investigations of the GABAergic system.

Materials and Methods

The study employed a single-blind design. Subjects were outpatients with the diagnosis of generalized anxiety disorder and panic-disorder according to DSM III (1980) criteria. Panic-disorder patients were accepted if they suffered generalized anxiety in addition to panic attacks. All patients were physically healthy and free of medication for a least 1 week

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Table 1. Effects of THIP on anxiety disorders: Total sample ($N = 8$)

	Baseline	Week 1 (placebo)	Week 2 (drug)	Week 3 (drug)
Mean physician's ratings ± SD				
Hamilton anxiety scale	21.6 ± 1.6	17.6 ± 1.6	12.0 ± 2.6	6.9 ± 1.9
Global ratings of generalized anxiety	2.6 ± 0.2	2.2 ± 0.1	1.9 ± 0.3	1.25 ± 0.4
Mean patient's ratings ± SD				
SCL-90R total score	119.4 ± 22.1	115.5 ± 22.1	95.9 ± 22.5	132.5 ± 40.0
Anxiety subscale	1.67 ± 0.4	1.50 ± 0.3	1.14 ± 0.3	1.30 ± 0.4
Somatic Symptoms Scale	17.2 ± 2.9	18.4 ± 2.6	17.4 ± 3.7	14.9 ± 2.9
Daily self-ratings of anxiety	–	37.2 ± 7.3	37.0 ± 8.2	23.9 ± 9.3

prior to the study. Women of childbearing potential were excluded.

The patient population consisted of eight subjects (five males, three females). Average age was 41.1 years (range 27–58 years) with an average education of 14.7 years (range 12–20 years). Three patients were diagnosed to have generalized anxiety disorder and five panic disorder. On the Eysenck Personality Inventory, the average neuroticism rating was 16.5 (range 7–22), average trait anxiety rating on the State-Trait Anxiety Inventory (Spielberger et al. 1970) was 51.6 (range 34–71), and the average Hamilton anxiety scale (Hamilton 1959) was 21.6 (range 13–27). One patient with low anxiety scores was included because of the chronicity of her condition.

The study lasted 4 weeks. After the initial evaluation, patients were placed on placebo for 1 week, then on THIP for 2 weeks. During week 4, patients again received placebo. Subsequently, all patients were followed with conventional treatment for at least 3 weeks.

Weekly physician's ratings included the Hamilton anxiety scale (Hamilton 1959), which rated psychic and physical symptoms of anxiety, and the global rating of generalized anxiety (a 4-point scale) (Hoehn-Saric 1982b).

Weekly patient's ratings were the State-Trait Anxiety Inventory state form (Spielberger et al. 1970), which measured 'psychic' aspects of anxiety, the Symptom Checklist (SCL-90R) (Derogatis 1975), which measured a cross-section of symptoms occurring in nonpsychotic conditions, the Somatic Symptoms Scale (Hoehn-Saric 1981), which measured somatic symptoms associated with anxiety, and the daily self-ratings of anxiety, which rated type, frequency, and severity of anxiety on a 1–100 scale.

Patients underwent a physical examination, routine blood examination including blood chemistry (SMA 6 and 12), and urinalysis at the time of the initial examination and after week 2 on active mediation. Blood pressure and pulse were recorded weekly.

At each session patients received medication in an envelope which was returned at the next visit. During week 1, patients received placebo that was identical in appearance to the active medication and were instructed to take one tablet three times a day. During week 2, the tablets were changed to THIP (5 mg) and the patients were advised to increase medication to two tablets (i.e., THIP 10 mg) three times daily if tolerated. During week 3, patients received THIP (10 mg tablets) to be taken one or two tablets three times daily as tolerated (10–20 mg 3 × day). Patients who were unable to tolerate more than 5 mg THIP during week 1 remained on 5 mg tablets during week 2. During the final week, patients received placebo and were asked to take the same number of tablets as during the previous week.

An analysis of variance for repeated means was calculated to examine overall changes. Orthogonal comparisons were employed to compare drug and placebo conditions.

Results

Dosage. During week 1, all patients initially increased the dose of THIP to 10 mg three times a day, but three of the eight patients subsequently reduced it to 5 mg. The average single doses during drug week 1 was 8.1 mg (5–10 mg). During week 2, all but one patient, who had strong side effects with 10 mg THIP, received 10 mg tablets of THIP. Seven patients increased to 20 mg THIP three times a day, but only one patient continued on this dosage for the entire week. The remaining patients returned to 10 mg three times a day. The average dose regularly taken during week 2 was 10.6 mg three times a day (range 5–20 mg).

Anxiolytic Effects of THIP. Three of the eight patients reported marked improvement on THIP, and two reported some improvement but complained of side effects. The remaining three patients felt that the side effects outweighed the possible benefit, and two patients dropped out of the study after week 2 on active medication. Table 1 presents the physician's ratings and patient's self-ratings durings during the baseline evaluation for all eight subjects, the first placebo week and the two subsequent weeks on THIP. Anxiety ratings decreased during placebo week, but decreased to a greater extent during the weeks on THIP.

Table 2 shows changes occurring in the six patients who completed the study. In these patients, the reduction of anxiety was most evident. Analysis of variance for repeated measures showed significant changes over time on the following ratings: Hamilton anxiety scale ($P < 0.002$); global ratings of generalized anxiety ($P < 0.02$); daily self-ratings of anxiety ($P < 0.04$). However, comparison of the 2 placebo weeks (the first preceding, and the second following 2 weeks of active drug treatment) revealed no significant differences on any of these measures. Ratings on the Hamilton anxiety scale were significantly lower during the drug weeks then during the placebo weeks on the total score ($P < 0.001$), the psychic subscale ($P < 0.01$), and the somatic subscale ($P < 0.01$). Global ratings of generalized anxiety were also lower during the drug weeks ($P < 0.01$). These ratings also declined significantly from the first to the second week on THIP ($P < 0.05$). Daily self-ratings of anxiety declined sig-

Table 2. Effects of THIP on anxiety disorders: study completers ($N = 6$)

	Baseline	Week 1 (Pl_1)	Week 2 (D_1)	Week 3 (D_2)	Week 4 (Pl_2)
Mean physician's ratings ± SD					
Hamilton anxiety scale	21.5 ± 1.9	17.7 ± 1.8	10.0 ± 2.8	4.3 ± 1.2	15.2 ± 2.8
Global ratings of generalized anxiety	2.3 ± 0.2	2.2 ± 0.1	1.7 ± 0.3	0.8 ± 0.4	2.0 ± 0.4
Mean patient's ratings ± SD					
SCL-90R total score	102.3 ± 25.7	100.5 ± 26.4	70.4 ± 21.5	83.8 ± 29.7	75.8 ± 27.4
Anxiety subscale	1.34 ± 0.4	1.28 ± 0.4	0.74 ± 0.3	1.1 ± 0.5	1.05 ± 0.4
Somatic Symptoms Scale	16.7 ± 3.1	16.5 ± 3.1	15.2 ± 4.5	11.5 ± 2.8	14.8 ± 4.3
Daily self-ratings of anxiety	—	30.5 ± 6.0	28.1 ± 6.3	11.1 ± 5.2	21.3 ± 5.9

Statistical analysis	Analysis of variance Week 1 to week 4		Orthagonal comparisons					
			Pl_1 vs. P_2		D_1 vs. D_2		Pl_{1+2} vs. D_{1+2}	
	F	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Hamilton anxiety scale								
Total score	7.84	< 0.002	0.84	NS	1.90	NS	4.39	< 0.001
Psychic subscale	6.44	< 0.005	0.92	NS	1.83	NS	3.87	< 0.01
Somatic subscale	4.18	< 0.03	0.29	NS	1.73	NS	3.07	< 0.01
Global ratings of generalized anxiety	5.13	< 0.02	0.46	NS	2.27	< 0.05	3.15	< 0.01
Daily self-ratings of anxiety	3.49	< 0.04	1.40	NS	2.58	< 0.05	1.36	NS

nificantly during the drug weeks ($P < 0.05$), but the difference between the drug and placebo weeks failed to reach significance. Changes on the SCL-90R and the Somatic Symptoms Scale failed to reach significance.

Physiological Effects. In general, THIP was tolerated well. Systolic blood pressure decreased by an average of 7.6 mm Hg from the placebo week to drug week 1 ($P < 0.10$), while the diastolic blood pressure did not change. Heart rate decreased by an average of 5.4 bpm from the placebo to drug week 1 ($P < 0.05$). No significant changes in blood pressure or heart rate occurred during the subsequent drug week. Except for a slight increase of eosinophils in two cases (6% and 8%), laboratory tests, including ECG, were essentially within normal limits at the end of drug week 2. No physical manifestations suggesting an allergic reaction were observed.

Side Effects. Side effects were common at dose levels of 10–20 mg (Table 3). Five of the patients complained of feelings of unreality, three of poor concentration, and one patient experienced dream-like illusions similar to those she had previously experienced during a high fever. Dizziness was reported by three patients, mild nausea by five, and feelings of giddiness or being off balance by three patients. Two patients experienced rapid fluctuation of anxiety symptoms while on medication, feeling better for 1 to 2 h and then worse. One patient complained of increased tension, irritability, and mild agitation. Some sleepiness was reported by most of the patients. None of these symptoms were sufficiently severe to discontinue the medication once a patient reduced the daily dosage. Two patients were sufficiently uncomfortable on THIP to request discontinuation of the medication after drug week 2. The side effects were not related to diagnostic subcategories.

Table 3. Side effects

	Number of patients
Sleepiness, mild	5
Sleepiness, moderate	2
Feeling of unreality	5
Poor concentration	3
Dream-like images (illusions)	1
Agitation	1
Dizziness	3
Nausea (mild)	5
Feeling off balance	3
Intermittent symptoms	2

Follow-Up. After the termination of the study, all patients were followed up for a least 3 weeks. One patient chose to stay off medication, one patient was placed on clorazepate, and the remaining six patients were prescribed alprazolam. Without exception, all patients preferred the conventional benzodiazepine medications, reporting greater anxiolytic effects with fewer side effects.

Discussion

The present study assessed the effects of THIP, a GABA agonist, on several measures of anxiety. Anxiety ratings began to decrease during placebo week 1 continued to decline during 2 weeks of THIP administration. A subsequent increase in anxiety ratings following replacement of THIP by placebo during the final week suggests that THIP had some anxiolytic effects. These effects were weak and appeared close to, or at drug levels that induced sedation and other undesireable side effects. Patients who subsequently received benzodiazepines, mainly alprazolam, reported the latter drugs more effective with fewer side effects than THIP.

With the side effects seen with the given dosages were not serious, they were disturbing to the patients. Sleepiness and drowsiness were noticed by most patients, and less frequently reported were mild nausea, difficulty concentrating feelings of depersonalization and derealization, giddiness, and agitation. In one case, transitory illusions and strong emotional lability were directly related to the higher dose of THIP. It appeared that the range between therapeutic dose levels of THIP and those which cause side effects and interfere with the anxiolytic action was very narrow. The rapid fluctuations between calmness and heightened anxiety reported by two patients could be attributed to the short half-life of THIP. The decline of average heart rate on THIP may be an intrinsic effect of the drug (Gillis 1982; H Lundbeck and Company 1981), or it could be secondary to the calming effects of THIP.

Panic-disorder patients were included in the sample if they suffered from generalized anxiety, because benzodiazepines decrease generalized anxiety despite their apparent failure to prevent the recurrence of anxiety attacks (Klein 1982). In our sample, THIP lowered generalized anxiety in patients of both diagnostic categories, but did not affect the number or the severity of panic attacks. However, the sample was too small and the duration of treatment too short to draw definite conclusions about the effects of THIP on panic attacks.

The degree to which the effects of THIP can be related to the action of GABA on the GABAergic system remains unknown. The pharmacology of THIP indicates that its effects are more limited than those of GABA and muscimol, perhaps due to its rigid molecular structure (Krogsgaard-Larsen and Arnt 1980) and selective binding to certain subtypes of the GABA receptor (Falch and Krogsgaard-Larsen 1982). On the other hand, the observed side effects of THIP were similar to those seen with other GABA agonists and GABA-mimetic drugs (Meldrum 1982): confusion, depersonalization, disorientation, and toxic psychosis occurred after administration of such drugs. While THIP produced only mild side effects, they were similar in quality to those of other GABA-mimetics. It appears that increased GABA levels, or a general stimulation of the GABAergic system, disrupt normal functions of the brain and that specific GABA subsystems, such as the GABA-benzodiazepine receptor complex, may be necessary for channeling GABA activities into circumscribed and organized functions.

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References

Cananzi AR, Costa E, Guidotti A (1980) Potentiation by intraventricular muscimol of the anticonflict effect of benzodiazepines. Brain Res 196:447–453

Cuomo V, Cortese I, Siro-Brigiani G (1981) Effects of muscimol alone and in combination with diazepam on shuttle-box performance in rats. Drug Res 31:1724–1726

Derogatis LR (1975) SCL-90R Clinical psychometric research. Baltimore

DSM III (1980): Diagnostic and statistical manual of mental disorders, 3rd ed. American Psychiatric Association, Washington DC, pp 225–239

Falch E, Krogsgaard-Larsen P (1982) The binding of the GABA agonist ^{3}H-THIP to rat brain synaptic membranes. J Neurochem 38:1123–1129

Gillis AR, Williford DJ, Dias Souza J, Quest JA (1982) Central cardiovascular effects produced by the GABA receptor agonist drug THIP. Neuropharmacology 21:545–547

Hamilton N (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55

H Lundbeck and Company (1981) THIP, LU2-030: Pharmacology, toxicity, pharmacokinetics and clinic. H Lundbeck, Copenhagen

Hodges HM, Green SE (1981) Evidence of a role for GABA in benzodiazepine effects on food preference in rats. Psychopharmacology 75:305–310

Hoehn-Saric R (1981) Characteristics of chronic anxiety patients. In: Klein DF, Rabkin J (eds) Anxiety: New research and changing concepts. Raven, New York, pp 399–409

Hoehn-Saric R (1982a) Neurotransmitters in anxiety. Arch Gen Psychiatry 39:735–742

Hoehn-Saric R (1982b) Comparison of generalized anxiety disorder with panic disorder patients. Psychopharmacol Bull 18:104–108

Klein DF (1982) Medication in the treatment of panic attacks and phobic states. Psychopharmacol Bull 18:85–90

Krogsgaard-Larsen P, Arnt J (1980) Pharmacological studies of interactions between benzodiazepines and GABA receptors. Brain Res Bull (Suppl) 2:867–872

Meldrum B (1982) GABA and acute psychosis. Psychol Med 12:1–5

Palfreyman MD, Schechter PJ, Buckett WR, Tell GP, Koch-Weser J (1981) The pharmacology of GABA-transaminase inhibitors. Biochem Pharmacol 30:817–824

Paul SM, Marangos PJ, Skolnick P (1981) The benzodiazepine-GABA-chloride ionophore receptor complex: Common site for minor transquilizer action. Biol Psychiatry 16:213–229

Rasmussen KJ, Schneider HH, Petersen EN (1981) Sodium valproate exerts anticonflict activity in rats without any concomitant rise in forebrain GABA level. Life Sci 29:2163–2170

Spielberger CS, Gorsuch RL, Lushene RE (1970) Manual for the State-Trait Anxiety Inventory. Psychologists Press, Palo Alto

Supavilai P, Karobath M (1980) The effect of temperature and chloride ions on the stimulation of ^{3}H-flunitrazepam binding by the muscimol analogues THIP and piperidine-4-sulfonic acid. Neurosci Lett 19:337–341

Tallman JF, Paul SM, Skolnick P, Gallager D (1980) Receptors for the age of anxiety: Pharmacology of the benzodiazepines. Science 207:274–281

Tamminga CA, Crayton JW, Chase TN (1979) Improvement of tardive dyskinesia after muscimol therapy. Arch Gen Psychiatry 36:595–598

Thiébot MH, Jobert A, Soubrié P (1980) Chlordiazepoxide and GABA injected into raphe dorsalis release the conditioned behavioural suppression induced in rats by a conflict procedure without nociceptive component. Neuropharmacology 19:633–641

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